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Iboga interactions with psychomotor stimulants: panacea in the paradox?

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Abstract

Currently, no effective therapy has been approved for the treatment of addiction to stimulant drugs (e.g., cocaine, amphetamine and its methylated derivatives). However, preclinical studies indicate that the naturally-occurring indole alkaloid, ibogaine, and a synthetic *iboga* alkaloid congener, 18-methoxycoronaridine (18-MC), attenuate stimulant self-administration in laboratory animals. The in vivo pharmacological interactions between *iboga* agents and stimulant drugs are unclear. Ibogaine enhances the increase in accumbal dopamine produced by the acute administration of stimulant drugs. Consistent with these data, both ibogaine and 18-MC potentiate the expression of stimulant-induced motor behaviors in acute and chronic stimulant-treated animals. To account for the paradox between their effects on self-administration and motor behavior, we proposed that *iboga* agents interfere with stimulant self-administration by increasing sensitivity to their psychomotor-activating effects. However, this interpretation is contradicted by very recent observations that 18-MC is without effect on the dopamine response to acute cocaine and that both ibogaine and 18-MC block the expression of sensitized levels of dopamine in the nucleus accumbens produced by chronic cocaine administration. Thus, a positive relationship exists between the effects of *iboga* pretreatment on stimulant-induced dopamine sensitization and stimulant self-administration behavior. These data indicate that *iboga* agents might attenuate stimulant self-administration by reversing the neuroadaptations theoretically implicated in drug craving and compulsive drug-seeking behavior. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The increasing illicit use of psychomotor stimulant drugs (including, cocaine, amphetamine and its methylated derivatives) is a significant public health concern worldwide. Despite this, and the considerable neuro-

biological knowledge relative to cocaine and the amphetamines, applicable medications for the treatment of stimulant addiction are not available. However, it has been proposed that an optimal strategy for treating cocaine addiction, which can be applicable to stimulant addiction in general, might involve the use of several medications that have different mechanisms of action, or several medications targeted at different aspects of the addiction problem (e.g., relapse, craving, etc.) (Klein, 1998).

Consistent with this position, the naturally occurring

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indole alkaloid, ibogaine (Fig. 1), was claimed to interrupt the “physiological and psychological aspects” of addiction to opiates (heroin), stimulants (cocaine and amphetamine), alcohol, cigarettes (nicotine) and of poly-drug abuse (United States patent numbers 4,499,096; 4,587,243; 4,857,523; 5,026,697; 5,124,994). Derived from the root bark of the West African shrub, *Tabernanthe iboga*, ibogaine appears to be unlike any known potential anti-addictive agent. A single oral treatment with ibogaine (6–19 mg/kg) is claimed to abolish drug craving and withdrawal symptoms for up to 6 months and repeated ibogaine treatments (a series of four oral administrations) are said to be effective at blocking craving and withdrawal for up to 3 years (e.g., Frenken, 2000; Sheppard, 1994). To a certain extent, ibogaine’s anti-addictive claims have been substantiated in preclinical studies. Both single and repeated doses of ibogaine can reduce the self-administration of cocaine (Glick et al., 1994; Serhsen et al., 1994) in rodents. These “therapeutic” effects were reported to last for at least 24 h, and up to several weeks in some rats (Glick et al., 1991). These times are well beyond the presence of the drug, or its active metabolite, noribogaine, in the brain (Hough et al., 1996; Pearl et al., 1997). A synthetic *iboga* alkaloid congener, synthesized by M. Kuehne and colleagues (University of Vermont), ($\pm$)-18-methoxycoronaridine (18-MC; Fig. 1) also decreases the self-administration of cocaine, in addition to other drugs of abuse, in rats (e.g., Glick et al., 1996, 1999). Similar to its parent compound, ibogaine, 18-MC reduces several signs of morphine withdrawal in physically dependent rats

(Rho and Glick, 1998). However, 18-MC exerts its “anti-addictive” effects without producing the side effects which have been associated with its parent compound, ibogaine (e.g., whole body tremors, ataxia, bradycardia, cerebellar neurotoxicity) (for reviews, Glick et al., 1999, 2000). Thus, 18-MC is a safer potential strategy than ibogaine for the treatment of psychomotor stimulant addiction (Glick et al., 1999).

The precise mechanisms of the anti-addictive action of ibogaine and 18-MC are not known. Consistent with their ability to target different aspects of addiction (including, drug-taking behavior and withdrawal signs), the receptor binding profiles for ibogaine and 18-MC are complex. Both ibogaine and 18-MC bind to the mu and kappa opioid receptors, as well as to the serotonin 5-HT₃ receptor. In addition, 18-MC binds with moderate affinity to the delta opioid receptor (Glick et al., 1999). In contrast, ibogaine shows binding affinity to the NMDA subtype of glutamate receptor, the sigma 2 receptor, the serotonin transporter, and the M2 subtype of muscarinic acetylcholine receptor (Glick and Maisonneuve, 1998). As indicated in Table 1, the affinities of ibogaine and 18-MC for these receptors are in the low micromolar range. In the rat, the terminal plasma half-lives of ibogaine and 18-MC are comparable, approximately 1 h (Glick et al., 1999). Although the receptor binding profile for ibogaine can account, in part, for its potential toxicity, it is difficult at this time to reconcile the receptor binding profiles of these two *iboga* agents with their protracted effects on drug self-administration or other drug-induced behaviors (e.g., locomotor hyperactivity).

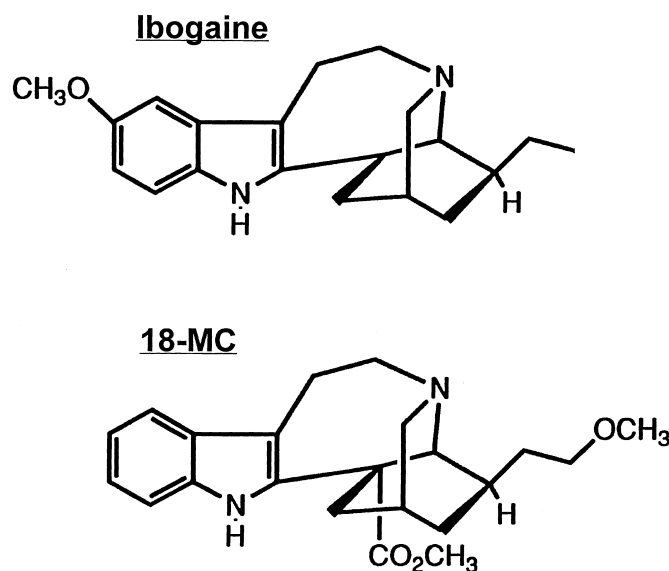


Fig. 1. A comparison of the chemical structures of the prototypical *iboga* alkaloid, ibogaine (top), and a synthetic *iboga* alkaloid congener, ($\pm$)-18-methoxycoronaridine (18-MC) (bottom).

Drug addiction is a disease characterized by compulsive drug seeking and repeated drug-taking behaviors (Jaffe, 1990). Thus, by virtue of their clinical indication, the efficacy of *iboga* compounds are assessed in individuals with repeated drug experience (e.g., Frenken, 2000; Sheppard, 1994). Related to this, the cellular underpinnings of the anti-addictive effects of *iboga* agents should be investigated necessarily in drug-experienced animals (for reviews, Fuchs et al., 1998; Kreek and Koob 1998; Markou et al., 1993; Roberts 1992). This is an important consideration given that the repeated administration of psychomotor stimulant drugs can produce enduring increases in sensitivity to certain drug effects, including motor hyperactivity and psychosis (e.g., Ellinwood et al., 1973; Robinson and Becker, 1986; Stewart and Badiani, 1993). Termed *sensitization*, this phenomenon has been characterized extensively both in human stimulant addicts (e.g., Angrist et al., 1974; Ellinwood et al., 1973) and in laboratory animals (e.g., Robinson and Becker, 1986). In humans, the expression of behavioral sensitization can persist for years after the cessation of drug administration (cf. Gold and Bowers, 1978), presumably reflecting persistent cellular neuroadaptations (e.g., Robinson and Becker, 1986; Kalivas et al., 1993; Kalivas and Stewart, 1991).

Some current theories of drug addiction argue that

the cellular neuroadaptations mediating behavioral sensitization are relevant to certain aspects of psychomotor stimulant addiction, for example, craving and psychosis (e.g., Kalivas et al., 1998; Robinson and Berridge, 1993; Robinson and Becker, 1986). The corollary of these sensitization theories of addiction is that compounds with anti-addictive properties should modulate the expression of sensitization produced by the chronic administration of psychomotor stimulant drugs. This paper will review our current understanding of the *in vivo* pharmacological interactions between the putative anti-addictive agents, ibogaine and 18-MC, and the sensitization produced by the repeated administration of psychomotor stimulant drugs. More specifically, this paper will highlight the similarities and differences between the effects of *iboga* pretreatment on the changes in brain and behavior produced by the acute and repeated administration of cocaine and the amphetamines.

2. Interactions between *iboga* agents and stimulant-induced behavioral sensitization

2.1. Locomotor hyperactivity

Locomotor hyperactivity serves as a reliable, objective measure of the psychomotor-activating effects of

Table 1

Interactions of ibogaine and 18-MC with the target sites listed below (values are $\mu\text{M } K_i$)

	Ligand	Tissue	($\pm$)-18-MC	Ibogaine
Kappa opioid	[3H]-U69593	Calf cortex	5.1 ± 0.50	2.2 ± 0.10
Mu opioid	[3H]-DAGO	Calf cortex	1.1 ± 0.30	2.0 ± 0.15
Delta opioid	[3H]-DPDPE	Calf caudate	3.5 ± 0.05	> 10
Nociceptin	[3H]-nociceptin	Bovine cortex	> 100	> 100
NMDA	[3H]-MK801	Bovine cortex	> 100	3.1 ± 0.30
D1	[3H]-SCH23390	Calf caudate	> 100	> 10
D2	[3H]- <i>N</i> -methyl-spiperone	Calf caudate	16 ± 0.60	> 10
D3	[3H]-7-OH-DPAT	Calf caudate	25 ± 2.5	70 ± 1.7
M1	[3H]-pirenzepine	Calf cortex	32 ± 3	16 ± 1.0
M2	[3H]-QNB	Calf cortex	> 100	31 ± 3.4
5-HT1A	[3H]-8-OH-DPAT	Rat hippocampus	46 ± 4.9	> 100
5-HT1B	[3H]-serotonin	Calf caudate	> 100	> 100
5-HT1C	[3H]-mesulergine	Calf cortex	> 100	> 100
5-HT1D	[3H]-serotonin	Calf caudate	> 10	> 100
5-HT2A	[3H]-ketanserin	Gf-6 cells	40 ± 3.4	16
5-HT2C	[3H]-mesulergine	J-1 cells	> 100	> 10
5-HT3	[3H]-GR-65,630	NG-108 cells	3.8 ± 0.067	2.6 ± 0.23
Sodium channel	[3H]-BTX-B	Bovine cortex	6.4 ± 0.68	3.6 ± 0.35
Sigma 1	[3H]-(+)-pentazocine	Calf caudate	> 100	2.5 ± 0.6
Sigma 2	[3H]-DTG	Calf hippocampus	13 ± 1.2	0.4 ± 0.036
GABA B	[3H]-GABA	Calf cortex	> 100	> 100
NE uptake	[3H]-nisoxetine	Bovine cortex	> 10	> 100
5-HT uptake	[3H]-paroxetine	Bovine brain stem	> 10	4.1 ± 0.83

stimulant drugs. Given that psychomotor-activation is one of the underlying factors responsible for the development and maintenance of addiction to stimulant drugs (e.g., de Wit, 1998; Morgan et al., 1993; Preston et al., 1992), it is possible that the anti-addictive effects of ibogaine, and related agents, involve the dampening of the psychomotor-activating properties of stimulant drugs. However, earlier studies in laboratory rodents indicated this was not the case; pretreatment with ibogaine (40 mg/kg; 19–24 h earlier) potentiated the acute locomotor responses to cocaine (Maisonneuve and Glick, 1992; Szumlinski et al., 1999a, 1999b) and *d*-amphetamine (Blackburn and Szumlinski, 1997; Maisonneuve et al., 1992). Ibogaine pretreatment shifted the dose-response curve for stimulant-induced locomotion to the left of vehicle-pretreated controls, indicating that the potentiation of total locomotor activity reflects an increase in the potency of cocaine to induce locomotion in acute stimulant-treated rats (Maisonneuve and Glick, 1992; Szumlinski et al., 1999a). This suggests that ibogaine might enhance cocaine-induced locomotion by increasing the bioavailability of cocaine to the brain. Ibogaine pretreatment has been shown to augment brain levels of amphetamine in acute amphetamine treated rats (Glick et al., 1992).

These data for ibogaine pretreatment are inconsistent with the idea that the anti-addictive effects of iboga pretreatment are related to an ability to decrease sensitivity to the psychomotor-activating effects of stimulant drugs. In fact, these data indicate the opposite, namely, that ibogaine pretreatment enhances sensitivity to the psychomotor-activating effects of the acute administration of stimulants. This finding seems counterintuitive given the putative anti-addictive efficacy of ibogaine, unless one considers that higher doses of psychomotor stimulant drugs can be anxiogenic in humans and become aversive (Cohen, 1972; Gold and Bowers, 1978). Therefore, to reconcile the apparent discrepancy between the locomotion and self-administration studies, it was proposed that ibogaine, and perhaps related agents, such as 18-MC, might exert their anti-addictive effects via a potentiation of the psychomotor-activating effects of stimulant drugs (Maisonneuve and Glick, 1992).

The first report which compared directly the effects of pretreatment with ibogaine and 18-MC (40 mg/kg, 19 h earlier) on stimulant-induced motor behavior demonstrated that these two *iboga* compounds produced virtually identical increases in the expression of locomotor hyperactivity in response to a moderately high dose of cocaine (20 mg/kg) (Maisonneuve et al., 1997). These findings indicated that ibogaine and 18-MC share a common pharmacological interaction with cocaine, at least in acutely treated rats, and supported the idea this interaction reflects an enhanced sensitivity to the psychomotor-activating effects of cocaine. To

demonstrate conclusively that 18-MC increased sensitivity to the locomotor-activating effects of cocaine (as per previous indications for ibogaine), a cocaine dose-response study was conducted. In contrast to ibogaine and to previous results for 18-MC, 18-MC (40 mg/kg; 19 h earlier) produced a non-significant shift to the left in the dose-response curve for acute cocaine-induced locomotion (Szumlinski et al., 2000d). Furthermore, in a subsequent study, pretreatment with 18-MC (40 mg/kg; 19 h earlier) did not alter significantly the dose-response curve for locomotor hyperactivity induced by the acute administration of methamphetamine (Fig. 2, left; Szumlinski et al., 2000a). These data indicate that 18-MC does not enhance the expression of stimulant-induced locomotor activity, at least in acute stimulant-treated rats. Consistent with these results, 18-MC pretreatment does not alter the extracellular levels of cocaine following its acute administration (Szumlinski et al., 2000d).

That ibogaine and 18-MC differentially altered the locomotor hyperactivity induced by the acute administration of stimulant drugs was not surprising. As summarized in Table 2, the effects of pretreatment with ibogaine and 18-MC differ with respect to a number of drug-related variables. Presumably, these discrepancies reflect differences in the receptor binding profiles between these drugs (see Table 1), differences in their protracted effects on the transmission of different neurotransmitters (as suggested by Wei et al., 1998), or both. Alternatively, the possibility exists that the ability of 18-MC to potentiate stimulant-induced locomotor hyperactivity depends on the novelty of the testing apparatus; 18-MC potentiated locomotor responding to cocaine in rats placed in the activity monitors for the first time (Maisonneuve et al., 1997), whereas 18-MC was without effect on locomotor responding to cocaine in rats well-habituated to the activity monitors (Szumlinski et al., 2000d). Placement into a novel environment can induce locomotor hyperactivity in rats, behavior which has been interpreted to reflect stress (cf., Kalivas and Stewart, 1991). Furthermore, rats injected acutely with stimulant drugs will display augmented responses to these drugs if the animal is tested in a novel environment, compared with a familiar or habituated environment (e.g., Bardo et al., 1990; Wise et al., 1996). Thus, it may be proposed that 18-MC pretreatment, rather than increasing sensitivity to the acute pharmacological effects of psychomotor stimulants, per se, 18-MC might increase sensitivity to a number of factors that impinge upon acute stimulant-induced psychomotor-activation, including stress and/or the context in which the stimulant is administered.

Given that chronic stimulant administration can produce a sensitization of brain and behavior, the

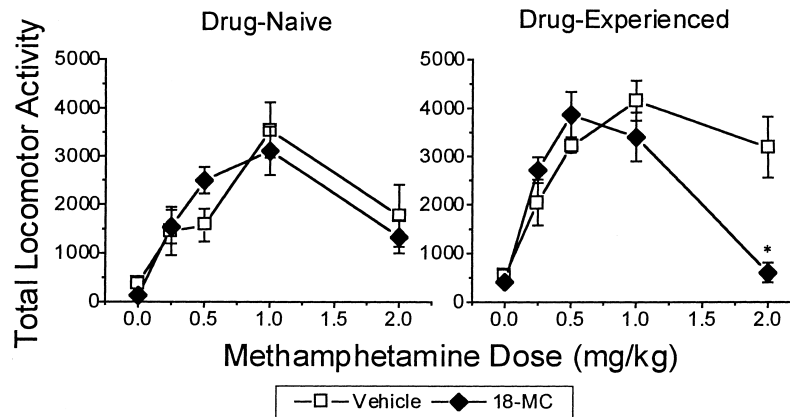


Fig. 2. The effects of pretreatment (40 mg/kg; 19 h earlier) with 18-MC (◆) or vehicle (□) on the dose-response functions for locomotion induced by the acute (left) or repeated (right) administration of methamphetamine (7×4 mg/kg). In all experiments, rats were placed in automated activity monitors immediately following methamphetamine injection (0–2.0 mg/kg) and locomotor activity was recorded for 2 h. 18-MC pretreatment shifted the dose-response function for methamphetamine-induced locomotion to the left of controls in rats treated repeatedly (Pretreatment by Dose interaction, $F(4, 50) = 6.33$, $P < 0.0004$), but not acutely (Pretreatment by Dose interaction, $F(4, 50) = 0.97$, $P = 0.45$) with methamphetamine. Symbols represent the mean total locomotor response of six to eight rats $\pm$ SEM. * $P < 0.05$ vs. vehicle, post-hoc tests.

possibility existed that pretreatment with ibogaine, and related agents, would differentially alter the psychomotor-activating effects of stimulant drugs as a function of previous drug experience. Indeed, an early study conducted by Blackburn and Szumlinski (1997) demonstrated that ibogaine pretreatment (40 mg/kg, 24 h earlier) attenuated the expression of locomotion in response to a moderate dose of amphetamine (1.5 mg/kg) in rats with repeated amphetamine experience. These findings were consistent with the available data at that time, namely, that ibogaine (1). decreased

cocaine-induced locomotion in mice with cocaine self-administration experience (Sershen et al., 1992), and (2). produced a greater decrease in morphine-induced locomotion in rats with previous morphine experience (Pearl et al., 1995). From these findings, it was suggested that ibogaine pretreatment might reverse the cellular neuroadaptations produced by repeated amphetamine administration (Blackburn and Szumlinski, 1997).

However, as evidenced in Fig. 2, the dose-response profile for stimulant-induced locomotion has an

Table 2

Comparison of the effects of pretreatment with ibogaine and 18-MC on the changes in brain and behavior produced by the acute administration of drugs of abuse

Drug of abuse	Dependent variable	Effect of ibogaine	Effect of 18-MC	References
Cocaine	locomotion (20 mg/kg)	increase	increase	Maisonneuve et al. (1997)
	potency to induce locomotion (0–40 mg/kg)	increase	no effect	
	dopamine in the nucleus accumbens	increase	no effect	Glick et al. (1999), Maisonneuve and Glick (1992)
Amphetamine	dopamine in the striatum	increase	no effect	Maisonneuve et al. (1992); Szumlinski et al. (2000a)
	potency to induce locomotion (0–2.0 mg/kg)	increase	no effect	
Methamphetamine	locomotion	decrease	increase	Maisonneuve et al. (1991); Pearl et al. (1995); Szumlinski et al. (2000b)
Morphine	dopamine in the nucleus accumbens	decrease	decrease	
	dopamine in the striatum	decrease	decrease	

inverted U-shape; lower doses of stimulants induce locomotor hyperactivity, whereas less locomotion is observed in response to higher stimulant doses. Thus, an alternative explanation for the results of Blackburn and Szumlinski (1997) was that ibogaine shifted the dose-response function for amphetamine-induced locomotion to the left, a finding which would be consistent with the increased sensitivity hypothesis. In support of this latter mechanism, a single dose study demonstrated that ibogaine pretreatment (40 mg/kg, 19 h earlier) induced the expression of locomotor sensitization in response to a low, locomotor-stimulatory, dose of cocaine (7.5 mg/kg) in rats with previous cocaine experience (Szumlinski et al., 1999a). Furthermore, when multiple test doses were employed, ibogaine did indeed shift to the left the dose-response profile for cocaine-induced locomotion in rats sensitized by previous cocaine experience (Szumlinski et al., 1999b). A similar increase in potency to induce locomotion was also produced by 18-MC pretreatment (40 mg/kg, 19 h earlier) in methamphetamine-sensitized rats (Fig. 2, right) (Szumlinski et al., 2000a). In contrast, 18-MC pretreatment (40 mg/kg, 19 h earlier) produced only a marginal effect on the potency of cocaine to elicit locomotor sensitization (Szumlinski et al., 2000d). However, an examination of the time-course of locomotion for the repeated cocaine-treated rats indicated that 18-MC produced a similar effect as ibogaine on the expression of locomotor activity across time (Fig. 3). As depicted in Fig. 3 (right), 18-MC pretreatment increased the duration of locomotor excitation expressed in response to a higher dose of cocaine (20 mg/kg) during the second hour of testing (Szumlinski et al., 2000d).

The studies of the interactions between *iboga* compounds and stimulant-induced locomotion provide clear evidence that pretreatment with *iboga* agents increases sensitivity to the locomotor-activating effects of stimulant drugs, an effect which can be augmented, rather than attenuated, in rats with previous stimulant experience. These data negate the possibility that the anti-addictive effects of *iboga* compounds are due to a dampening of the psychomotor-activating effects of stimulant drugs. Instead, they lend support to the possibility that the anti-addictive effects of *iboga* compounds might be related to their ability to potentiate stimulant-induced psychomotor activation, particularly in individuals with previous drug experience.

2.2. Stereotypy

The administration of higher stimulant doses can induce repetitive, focused behaviors (*stereotypies*), the expression of which can be physically incompatible with locomotion (e.g., focused sniffing, grooming, gnawing) (Creese and Iversen, 1972; Glick, 1972). Furthermore, the repeated administration of stimulant drugs can induce a switch from locomotor hyperactivity to stereotypy in response to lower doses of stimulant drugs or induce the sensitization of stereotypic behavior in response to higher stimulant doses (e.g., Kalivas et al., 1988; Segal, 1975). If pretreatment with *iboga* agents increases sensitivity to the psychomotor activating effects of stimulant drugs, then rats pretreated with *iboga* compounds should display higher levels of stereotypic behavior, compared with vehicle-pretreated animals. Indeed, the results of the locomotor studies to date (Blackburn and Szumlinski,

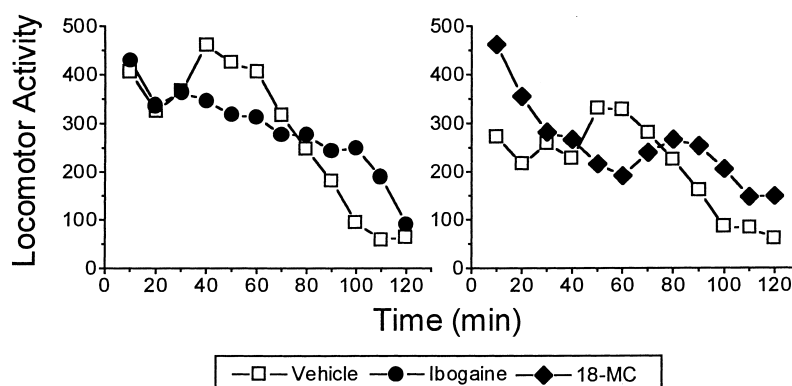


Fig. 3. Comparison of the effects of pretreatment (40 mg/kg; 19 h earlier) with the *iboga* agents, ibogaine (●), 18-MC (◆) or their respective vehicles (□) on the time-course of locomotion induced by 20 mg/kg cocaine (5×15 mg/kg) in rats with repeated cocaine experience (5×15 mg/kg). Both ibogaine and 18-MC pretreatment altered the expression of locomotor activity across time; compared with vehicle controls, these *iboga* agents enhanced the duration of locomotor excitation during the second hour post-cocaine [for ibogaine: pretreatment by time interaction, $F(11, 77) = 2.57$, $P < 0.01$; for 18-MC, main effect of Pretreatment, $F(11, 110) = 2.40$, $P < 0.02$]. Symbols represent the mean total locomotor response of six to eight rats.

1997; Szumlinski et al., 1999b, 2000a, 2000d) provide indirect evidence for such a possibility; sensitized rats, pretreated with either ibogaine or 18-MC, display lowered levels of locomotor activity in response to higher test injections of methamphetamine (2 mg/kg; Fig. 2) and cocaine (20 mg/kg; Fig. 3).

To directly address this issue, a series of experiments were conducted in parallel with the locomotor studies, in which the stereotypic behaviors of the animals were rated using traditional scoring methods (for cocaine: Kalivas et al., 1988; for methamphetamine: Cresse and Iversen, 1972; Ujike et al., 1992). As depicted in Fig. 4, both ibogaine and 18-MC pretreatment (40 mg/kg, 19 h earlier) promoted high levels of stereotypic behavior in response to the highest doses tested in the locomotor studies for both cocaine (top; Szumlinski et al., 1999c, 2000d) and methamphetamine (bottom; Szumlinski et al., 2000a). Furthermore, the enhancement of stereotypy produced by *iboga* pretreatment was observed in rats treated either acutely or repeatedly with the stimulant.

Such findings demonstrate that the locomotor-attenuating effects of pretreatment with *iboga* compounds can be attributed to an enhancement of the stereotypic effects of stimulant drugs at higher stimulant doses in rats repeatedly treated with either cocaine or the amphetamines. These data are conclusive evidence that *iboga* pretreatment increases the intensity of the psychomotor-activating effects of both cocaine and the amphetamines, and thus, provide further support for the hypothesis that the anti-addictive effects of *iboga* pretreatment might be related to an ability to enhance sensitivity to the psychomotor-activating effects of stimulant drugs.

3. Interactions between *iboga* agents and stimulant-induced dopamine sensitization

The phenomenon of behavioral sensitization produced by the repeated administration of drugs of abuse is used as an animal model for the investigation

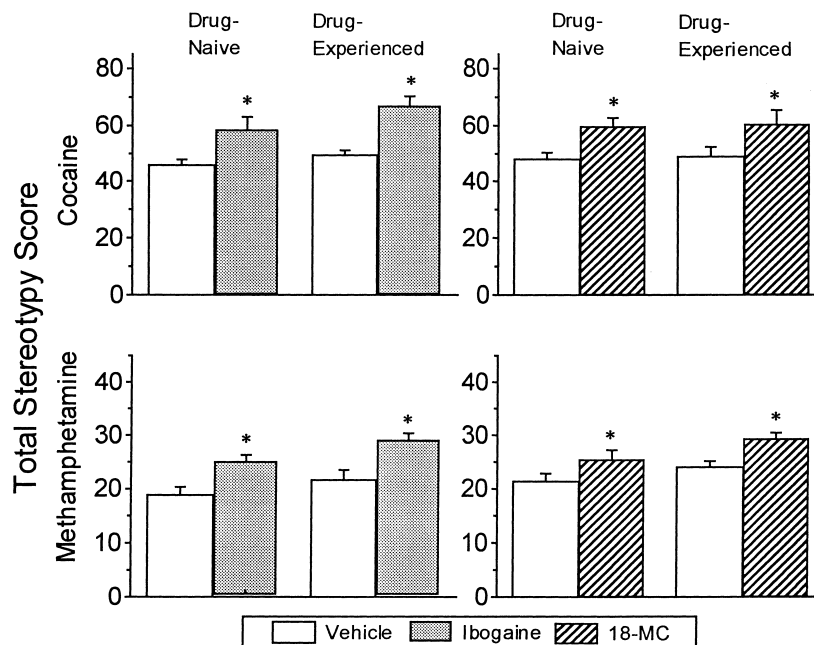


Fig. 4. The effects of pretreatment (40 mg/kg; 19 h earlier) with the *iboga* agents, ibogaine (left), 18-MC (right) or their respective vehicles on the expression of stereotypic behaviors induced by the acute or repeated administration of cocaine (top) and methamphetamine (bottom). In all experiments, rats were placed in clear cylindrical cages immediately following stimulant injection and stereotypy behavior was scored for every 20 min for a 2 h period, using the behavioral rating scales of Kalivas et al. (1988) for cocaine, and Creese and Iversen (1974) and Ujike et al. (1996) for methamphetamine. In both acute and repeated cocaine-treated rats, both ibogaine (main effect of pretreatment, $F(1, 44) = 11.05$, $P < 0.002$) and 18-MC (main effect of pretreatment, $F(1, 40) = 57.00$, $P < 0.0001$) potentiated the expression of stereotypy. Virtually identical effects were observed for methamphetamine-induced stereotypy (for ibogaine: main effect of pretreatment, $F(1, 38) = 20.80$, $P < 0.001$; for 18-MC: main effect of Pretreatment, $F(1, 40) = 7.85$, $P < 0.008$). Bars represent the mean total stereotypy response of six rats $\pm$ SEM. * $P < 0.05$ vs. vehicle, post-hoc tests.

of cellular neuroadaptations which may be relevant to certain aspects of psychomotor stimulant addiction, for example, craving and psychosis (e.g., Kalivas et al., 1998; Robinson and Berridge, 1993; Robinson and Becker, 1986). One neuroadaptation which has received extensive experimental attention is the sensitization of neurotransmission in the dopamine neurons that originate in the ventral tegmental area of the mid-brain and project to various forebrain structures, including the nucleus accumbens (the mesolimbic dopamine system) (for review, Kalivas et al., 1993). A wealth of evidence implicates the mesolimbic dopamine transmission in the mediation of incentive motivation/reward, not only for drugs of abuse, but for other primary reinforcers, such as food and sex (for reviews see: Berridge and Robinson 1999; Blackburn et al., 1992; Fibiger and Phillips, 1986; Mogenson and Phillips 1976; Wise and Bozarth, 1987). Furthermore, mesolimbic dopamine transmission is considered a critical mediator of drug-induced motoric behavior (for review see Kalivas and Stewart, 1991; Kalivas and Nakamura 1999) and dysregulation in mesolimbic dopamine function has been implicated in both idio-

pathic and stimulant-induced psychosis (e.g., Angrist et al., 1974; Ellison, 1994; Lieberman et al., 1990). Given that pretreatment with *iboga* compounds augmented the psychomotor activation produced by cocaine and the amphetamines, it was hypothesized that the enhancement in sensitivity to stimulant-induced psychomotor hyperactivity was related to an ability to potentiate the dopamine response to stimulant drugs in the mesolimbic system.

In support of this hypothesis, early in vivo microdialysis studies demonstrated that pretreatment with ibogaine (40 mg/kg, 19 h earlier) potentiates the dopamine response to an acute injection of both cocaine (Maisonneuve and Glick, 1992) and *d*-amphetamine (Maisonneuve et al., 1992). As can be observed in Fig. 5 (left), more recently, neither ibogaine nor 18-MC pretreatment (40 mg/kg, 19 h earlier) was found to produce a statistically significant effect on the dopamine response in the nucleus accumbens to an acute injection of cocaine (Glick et al., 1999; Szumlinski et al., 2000c; Szumlinski et al., 2000d), although *iboga* pretreatment enhanced the stereotypic responses to cocaine in these same animals (compare Figs. 5 and 6).

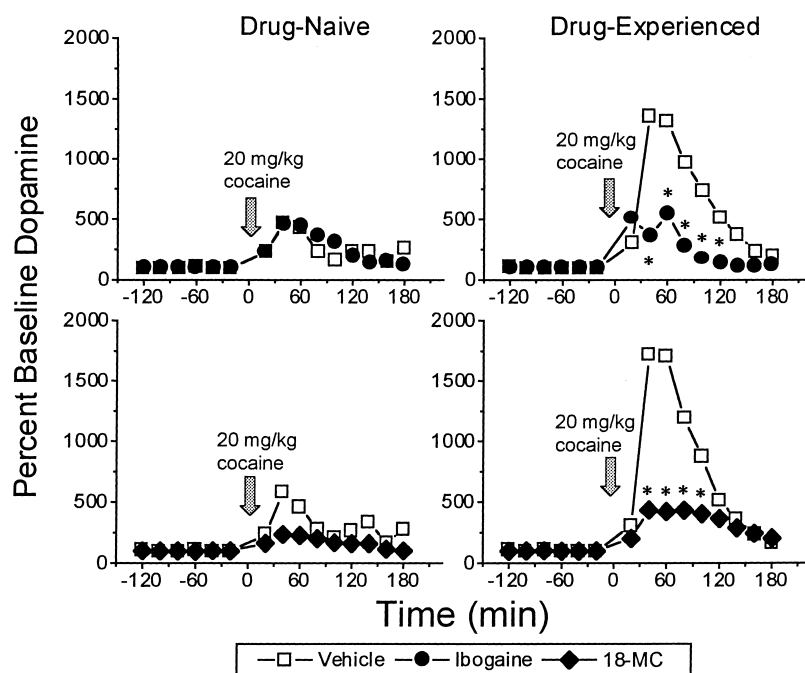


Fig. 5. The effects of pretreatment (40 mg/kg; 19 h earlier) with the *iboga* agents, ibogaine (●), 18-MC (◆) or their respective vehicles (□) on the percent increase above baseline in dopamine in the shell of the nucleus accumbens produced by cocaine in rats treated either acutely (left) or repeatedly (right) with cocaine. In both experiments, baseline dialysate samples (volume/sample = 20 μ l) were collected for 2 h and then the animals were injected with cocaine (20 mg/kg). Dialysate samples were collected for 3 h following injection. Pretreatment with either ibogaine or 18-MC abolished the sensitized dopamine response to cocaine in rats with repeated cocaine experience, without altering the dopamine response to cocaine in rats receiving cocaine for the first time [for ibogaine: chronic treatment by pretreatment by time interaction, $F(14, 336) = 3.32$, $P < 0.0001$; for 18-MC: chronic treatment by pretreatment by time interaction, F (data points represent the means of six to nine rats $\pm$ SEM). * $P < 0.05$ vs. vehicle, post-hoc tests.

The nucleus accumbens can be divided anatomically into at least two distinct compartments, the core and the shell, which differ in both their anatomical connectivity (e.g., Jongen-Relo et al., 1993) and their function (Ikemoto and Panksepp, 1999; Sokolowski and Salamone, 1998). Longer microdialysis probes (3 mm) were used in the earlier microdialysis studies (e.g., Maisonneuve and Glick, 1992); consequently, dopamine was sampled from both the core and shell regions of the nucleus accumbens. However, more recent studies employed shorter microdialysis probes (2 mm), which restricted the sampling of dopamine to the shell of the nucleus accumbens only (e.g., Szumlinski et al., 2000d). Therefore, differences in the origin of the dopamine (core vs. shell) may account for differences observed between the two sets of microdialysis studies. In support of this, Cadoni and colleagues have reported differential effects of chronic drugs of abuse on dopamine transmission in the core and shell of the nucleus accumbens (e.g., Cadoni et al., 2000). Given the possibility that psychomotor stimulant drugs might differentially alter dopamine transmission in the core and shell of the nucleus accumbens, we suggest that the enhancement of stimulant-induced psychomotor

activation by ibogaine, and related agents, may be related to their interactions with dopamine transmission in the core of the nucleus accumbens, rather than in the shell region.

This suggestion is supported by the observations that both ibogaine and 18-MC (40 mg/kg, 19 h earlier) completely block the expression of dopamine sensitization in the shell of the nucleus accumbens produced by repeated cocaine administration (Szumlinski et al., 2000c). As is clear from Fig. 5 (right), the blockade of dopamine sensitization by *iboga* pretreatment was coincident with enhanced levels of cocaine-induced stereotypy. Thus, in contrast to our original expectations, the ability of *iboga* agents to potentiate the expression of stimulant-induced sensitization of psychomotor activation appears to be unrelated to an enhancement of mesolimbic dopamine sensitization (at least in the shell of the nucleus accumbens) and implicates interactions between *iboga* agents and cocaine in brain regions other than the shell of the nucleus accumbens in the sensitization of the psychomotor activating effects of psychomotor stimulant drugs.

Interestingly, the blockade of dopamine sensitization in the shell of the nucleus accumbens produced by

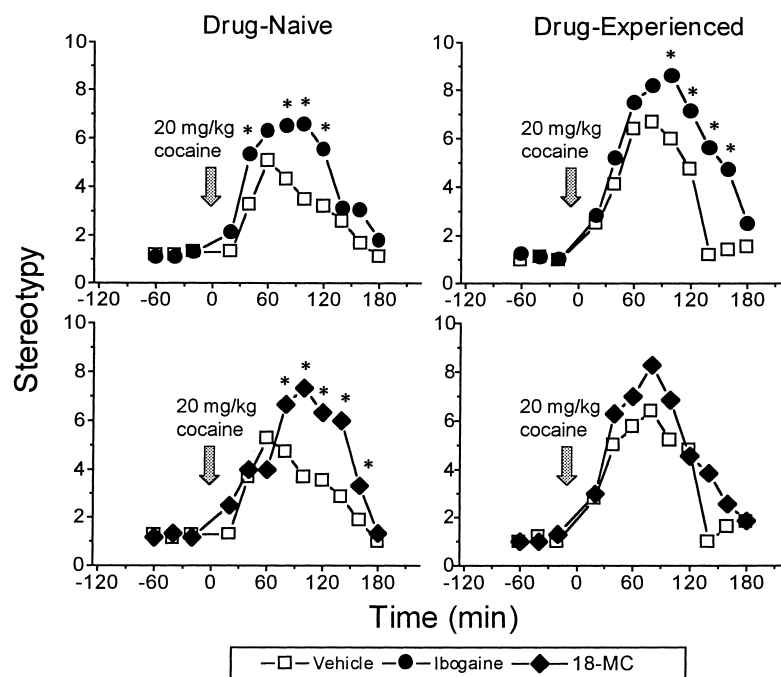


Fig. 6. The effects of pretreatment (40 mg/kg; 19 h earlier) with the *iboga* agents, ibogaine (●), 18-MC (◆) or their respective vehicles (□) on the time-course of stereotypy expressed by the acute (left) and repeated (right) cocaine treated rats in the microdialysis study (see Fig. 5) in response to cocaine (20 mg/kg). Stereotypic behaviors were scored for 3 h following injection. Ibogaine potentiated significantly the expression of stereotypy in rats treated either acutely or repeatedly with cocaine (Pretreatment by Time interaction, $F(12, 132) = 3.14$, $P < 0.01$). A similar effect was observed for 18-MC pretreatment (Pretreatment by Time interaction, $F(12, 132) = 5.00$, $P < 0.0001$). Data points represent the means of six to nine rats $\pm$ SEM. * $P < 0.05$ vs. vehicle, post-hoc tests.

iboga pretreatment is completely consistent with current sensitization theories of drug addiction. These theories posit that drug craving and drug-seeking result from the sensitization of the incentive motivational properties of drugs of abuse and drug-related cues, which is mediated presumably by a sensitization of mesolimbic dopamine transmission (e.g., Kalivas et al., 1998; Robinson and Berridge, 1993). Thus, the results of these recent microdialysis studies provide a plausible mechanism through which ibogaine and related agents might exert their anti-addictive effects. Namely, *iboga* compounds might attenuate the reinforcing efficacy of psychomotor stimulant drugs and drug-related cues. In support of this possibility, pretreatment with 18-MC blocks the sensitized dopamine response in the shell of the nucleus accumbens to morphine (Szumlinski et al., 2000b) and shifts the dose-response function for morphine self-administration downwards (Maisonneuve and Glick, 1999).

4. Discussion and conclusions

The naturally-occurring indole alkaloid, ibogaine, and its synthetic derivative, 18-MC, both attenuate the self-administration of psychomotor stimulant drugs. The precise mechanism(s) through which these compounds exert their “anti-addictive” effects are uncertain; however, it is clear from the anecdotal reports in humans that ibogaine can target various aspects of addiction, ranging from drug craving to withdrawal. We have argued in the past that the complex receptor pharmacology of ibogaine and related compounds may contribute to their unique ability to interrupt the many facets of stimulant addiction (e.g., Glick et al., 1999, 2000). The results of the studies presented in this paper provide insight into other explanations for the anti-addictive efficacies of ibogaine and related *iboga* compounds. Firstly, these studies clearly demonstrate that pretreatment with *iboga* agents does not attenuate the psychomotor activating effects of stimulant drugs. In fact, these studies clearly demonstrate that pretreatment with *iboga* agents increase the intensity of the psychomotor activating effects of stimulant drugs, at least in rodents. Thus, it is not likely that the therapeutic effects of these drugs involve a dampening of the psychomotor activating effects of stimulant drugs. Rather, these results indicate that the therapeutic effects of *iboga* agents probably involve a potentiation of these subjective effects, rendering subsequent self-administration of these drugs aversive.

Secondly, these studies clearly demonstrate that pretreatment with *iboga* agents can reverse one of the neuroadaptations implicated in the mediation of various aspects of addiction, namely dopamine sensitization in the mesolimbic dopamine system. Thus, the therapeutic

effects of ibogaine and related agents may involve a reversal of the pathological elevation in the incentive salience of stimulant drugs and their related cues, a hall-mark feature of drug addiction.

Thirdly, these studies clearly demonstrate that a dissociation exists between the effects of iboga pretreatment on stimulant-induced psychomotor activation and stimulant-induced neuroadaptations in the mesolimbic dopamine system (at least in the shell of the nucleus accumbens). These data suggest that the behavioral changes produced by repeated psychomotor stimulant administration reflect adaptations in more than one neurotransmitter system in the brain (e.g., Kalivas and Stewart, 1991; Kalivas et al., 1993). Moreover, these data indicate that *iboga* compounds are capable of interacting with multiple neuroadaptations produced by repeated stimulant administration. We suggest that it is precisely the ability of ibogaine and related agents to exert differential and complex effects on the neuroadaptations produced by chronic psychomotor stimulant administration that underlies their unique potential to interrupt addiction to these drugs.

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